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Letter to the Editor

Cevimeline Reduced Mouth Dryness and Increased Salivary Flow in Patients with Xerostomia Complicating Chronic Graft-versus-Host Disease

The mouth is affected in 75% to 85% of patients with chronic graft-versus-host disease (cGVHD) after allogeneic hematopoietic cell transplantation and ranks second behind the skin in order of prevalence of organ involvement [1]. Labial salivary gland biopsies show evidence of immunologically mediated destruction with lymphocytic infiltration [2]. Patients with cGVHD of the mouth frequently have xerostomia, which can be a distressing condition causing taste alterations, difficulty with chewing and swallowing, and anorexia, all potentially contributing to nutritional deficits and undesired weight loss [3,4]. In addition, the oral mucosa becomes susceptible to infection by *Candida albicans*, and overgrowth of procariogenic bacteria accelerates dental decay [5]. Xerostomia may have a greater effect for patients with cGVHD because of additional oral complications such as lichenoid and hyperkeratotic mucosal lesions, pseudomembranes, ulcers, and infections [6].

The Ancillary and Supportive Care Working Group of the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in cGVHD has concluded that the procholinergic agents pilocarpine and cevimeline, which are approved for symptomatic treatment of xerostomia associated with Sjögren syndrome, can be considered optional therapy for cGVHD-associated xerostomia [7]. In a small open-label, uncontrolled study, treatment with pilocarpine significantly improved objective and subjective measurements of salivary function in 6 patients with cGVHD-related xerostomia [8]. The relative selectivity of cevimeline for the M1 and M3 muscarinic receptors [9] may make it a preferred agent for use in patients with cGVHD.

Three patients at the Fred Hutchinson Cancer Research Center, Seattle, were enrolled in an open-label trial of cevimeline for cGVHD-associated xerostomia and completed treatment before the trial's premature termination due to slow accrual. The primary outcome measurement was the patient's final global evaluation of xerostomia as better, much better, worse, much worse, or unchanged after 10 weeks of treatment. Secondary outcome measurements included the patient's evaluation of separate symptoms using a 100-mm visual analog scale and unstimulated salivary flow 1.5 to 2.5 hours after the administration of a dose of cevimeline. Cevimeline was given at a dosage of 15 mg 3 times a day for 2 weeks, then 30 mg 3 times a day, and then 45 mg 3 times a day for the final 4 weeks of the study, if no improvement and no dose-limiting toxicity were seen at the end of week 6.

The experience of these 3 patients (Table 1), who each had persistent xerostomia symptoms despite an adequate trial of altered systemic or topical immunosuppressive therapy, indicates that cevimeline may be a useful ancillary therapy for xerostomia associated with cGVHD. All 3 patients reported improvement in the global evaluation of dry mouth, and 2 had increased unstimulated salivary flow after 10 weeks of treatment. In 1 patient, clinically significant and probably treatment-related adverse events developed on the last day of the 10-week study period. Symptoms of wheezing and eye discomfort may have been attributable to excessive systemic cholinergic effects at the highest dosage. No clinically significant abnormalities in vital signs, electrocardiograms, or laboratory values were detected during treatment with cevimeline.

The experience of these 3 patients confirms the potential benefit of cevimeline for treating cGVHD-associated xerostomia, and we recommend the standard approved dosage of 30 mg 3 times a day. Larger studies are warranted to confirm efficacy and safety in this population.

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Table 1. *Characteristics and Responses of the 3 Study Participants**

Characteristics	Data		
	Patient 1	Patient 2	Patient 3
Gender	Male	Male	Male
Diagnosis	MDS	AML	AML
Baseline demographics			
Age at study entry (y)	57	25	47
Duration of cGVHD (mo)	4	84	12
Prior sites of cGVHD	Skin, mouth	Skin, eyes, mouth	Skin, eyes, mouth, gut
Oral mucosal exam			
Erythema	Yes	Yes	Yes
Atrophy	Yes	Yes	Yes
Lichenoid striae	Yes	Yes	Yes
Hyperkeratotic plaques	Yes	No	Yes
Extensive dental caries	Yes	No	No
Saliva	Visibly reduced	Scant and foamy	Visibly reduced
Prior therapies (duration)			
First	P + CSP (6 wk)	P + CSP (18 mo)	P + CSP (12 mo)
Second	P + CSP + oral AZA or DEXA rinses (6 mo)	None (lost to follow-up for 2 y)	P + CSP, oxycodone + paroxetine (4 mo)
Third	P + TAC + SIR (6 wk)	CSP and AT (7 wk)	None
Cevimeline therapy†			
Days 1-14	15	15	15
Days 15-42	30	30	30
Days 43-70	30	45	30
Global xerostomia evaluation			
Day 14	Better	No change	Better
Day 42	Much better	Better	Better
Day 70	Much better	Better	Much better
Unstimulated salivary flow (g)‡			
Baseline	3.87	1.56	0.32
Day 14	6.66	1.51	0.95
Day 42	8.88	1.38	1.28
Day 70	11.21	1.32	1.77
Xerosis questionnaire (day 70)			
Ability to speak without drinking liquids improved	Yes	Yes	Yes
Fluid intake frequency decreased	Yes	No	No
Chewing improved	Yes	Yes	Yes
Swallowing improved	Yes	Yes	Yes
Broadened food choices	Yes	—	—
Decreased oral sensitivities	Yes	Yes	—
Decreased mouth sores	Yes	—	—
Improved sleep	Yes	Unchanged	Yes (but variable)
Decreased use of AT	Yes	Yes	—
Comments	Dry mouth recurred immediately after study ended; cevimeline was then resumed for another 2 y	Wheezing and eye discomfort at day 70 resolved when cevimeline stopped, but xerostomia recurred	Dry mouth recurred after study ended; patient was treated with a short course of oral DEXA rinses and resumed cevimeline for several months

*AML indicates acute myelogenous leukemia; AT, artificial tears; AZA, azathioprine; CSP, cyclosporine; DEXA, dexamethasone; MDS, myelodysplastic syndrome; P, prednisone; SIR, sirolimus; TAC, tacrolimus.
†Milligrams, oral, 3 times daily.
‡Amount of saliva collected over a period of 6 minutes.

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Paul A. Carpenter, MD
Mark M. Schubert, MD
Mary E. D. Flowers, MD
Fred Hutchinson Cancer Research Center
Clinical Research Division
Seattle, Washington

University of Washington
Seattle, Washington